清華大學
當代生命科學課程
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新藥免疫療法
發展治療哮喘與過敏的抗體藥物

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我們應重視生命科學的跨領域教學

新竹清大與北京清大領先世界發展用於工學院科系的生命科學教科書
Allergy: a very prevalent modern malady

- Allergic asthma
- Atopic dermatitis
- Allergy to latex
- Others

• Allergic rhinitis
• Food allergy
• Allergy to drugs

1819 – the first description of a hay fever-like syndrome

Today – 20 to 40% of populations in economically advanced countries
Allergy: vast, diverse medical fields

- Cared by doctors of different specialties
- Various societies, diverse journals
- Administered by NHLBI, NIAID, NIAMS in NIH, USA

Common drugs used for severe patients: corticosteroids

- High-dose corticosteroids have serious side effects.
- Some patients are still not controlled.
"Skewed Antigen Exposure" Theory

Cumulated environmental changes, skewed antigen exposure, and the increase of allergy.
The most common allergens in our “artificial” world.

Dust mites

Pollens

In “bio-deprived” indoor space, mites become the dominant antigen.

Sugi pollens are the dominant outdoor antigen in Japan.
Anti-IgE idea: inspiration from OKT3


Found OKT3 targets TCR in Ortho

→→→→

Can anti-IgE target IgE-BCR?

1986 1986

Invented antibody matrix in Centocor

1981 1985 1985

Invented anti-IgE approach

Chang et al. PNAS 78 (1981)


1987

OKT3 (Orthoclone) targets TCR.

Founded Tanox to develop microarray technol
Major steps in IgE-mediated allergic pathway

Induction/Sensitization

1. Allergens activate resting IgM/IgD B cell.
2. mIgE+ B cell.
3. IgE-plasma cell.
4. IgE binds to allergens.

Triggering

- Histamine
- Leukotrienes
- Tryptase

Manifestation

- Inflammation
- Bronchoconstriction
- Allergic rhinitis
- Asthma
- Anaphylaxis

Most current drugs work here.
Our goal: to targets IgE and mIgE-B cells

An ordinary anti-IgE is a super sensitizer.

What was the prior art?
The binding specificities of a therapeutic anti-IgE

A billion-dollar idea!
Process for developing a therapeutic anti-IgE mAb

• Develop mouse antibodies with the desired specificities by serial screening – using hybridoma methodology

• Humanize the antibodies – using genetic engineering tools

• Develop the manufacturing process
  - expressed by CHO cells
  - in serum-free medium in 12,000L tanks
  - 3-5 g/L
The binding site of anti-IgE on CH3 of IgE

Structural basis of the binding specificities of anti-IgE

From Wright & Lim, Protein Eng 11 (1998)

The binding sites of FcεRI, FcεRII, and anti-IgE overlap.
Basophils cells are armed.

Antigens are mopped up.
Basophils are desensitized.

Before and after anti-IgE treatment

Hsu et al Int Immunopharmacol (2010)
Multiple, immunoregulatory actions of anti-IgE

At several points in the early part of the IgE pathway
Anti-IgE program: it has taken 23 years.  
(It will take 5-10 more years.)

G. Johansson discovered IgE in 1967.  
( In 2007 AAAAI meeting)
## Anti-IgE: potentially a treatment platform

<table>
<thead>
<tr>
<th>Disease</th>
<th>Efficacy</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic asthma (&gt;12y)</td>
<td>✓</td>
<td>approved</td>
</tr>
<tr>
<td>Allergic asthma (pediatric)</td>
<td>✓</td>
<td>approved in EU</td>
</tr>
<tr>
<td>Allergic rhinitis (seasonal)</td>
<td>✓</td>
<td>multiple phase III done</td>
</tr>
<tr>
<td>Allergic rhinitis (perennial)</td>
<td>✓</td>
<td>multiple phase III done</td>
</tr>
<tr>
<td>Peanut allergy</td>
<td>✓</td>
<td>one phase II done</td>
</tr>
<tr>
<td>Latex allergy</td>
<td>✓</td>
<td>one phase II done</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>positive</td>
<td>many case series</td>
</tr>
<tr>
<td>11 other allergic diseases</td>
<td>positive</td>
<td>case series</td>
</tr>
</tbody>
</table>
Leaders were skeptical of anti-IgE approach.

Whether IgE is involved in the pathogenesis of asthma was not clear.

Leaders voiced that anti-IgE is a promising approach.

It was confirmed that IgE is involved in the pathogenesis of asthma.

(same journal)
The evaluation by users of major asthma drugs

Data from WebMD  http://www.webmd.com/drugs/index-drugs.aspx
39 Xolair users made evaluation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xolair</td>
<td>4.55</td>
<td>4.53</td>
</tr>
<tr>
<td>Singulair</td>
<td>3.71</td>
<td>3.00</td>
</tr>
<tr>
<td>Prednisone</td>
<td>3.45</td>
<td>2.62</td>
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<tr>
<td>Albuterol</td>
<td>3.82</td>
<td>3.61</td>
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<tr>
<td>Advair</td>
<td>4.24</td>
<td>3.69</td>
</tr>
<tr>
<td>Symbicort</td>
<td>4.18</td>
<td>3.71</td>
</tr>
</tbody>
</table>

Full score 5

Note: the scores on ease to use not shown
Comments from patients using Xolair

- Thanks for making this product!!!
- I felt great taking it.
- A miracle drug (5 patients said this.)
- Xolair changed my life.
- If I had not been put on the Xolair could likely be dead by now.
- Xolair is the best Christmas present.
- The medication has been a God-send.
- This is magic medicine!
- It truly changed my life.
We need medicine in addition to omalizumab.

**Anti-IgE**
- Approved
- Omalizumab (Trade name Xolair)

**Anti-εmX**
- In research

- For patients with IgE higher than 700 IU/ml
- To reduce the amount of antibodies
- To provide medicine to patients broadly

Inhibiting mlGε B cells without binding to free IgE
Human mIgE contains “CεmX”.

ε CH4 exon is spliced to membrane exons in two ways.

CεmX: a 52 a.a. domain

Long form is 1000 times more than short form.
"CεmX" discovery offers new therapeutic strategies.

Approaches based on CεmX
- Anti-CεmX antibodies
- Vaccines based on CεmX

Alleles found on CεmX
- 16V and 16L

Sequences unique in protein databanks
Human $\epsilon mX$-harboring transgenic mice

Natural $mIgE$

$\epsilon mX$ mouse
Anti-IgE helps severe patients.

Teresa Deng died of asthma in 1995.

With Xolair, many severe asthma patients can now live normal lives.